American Journal of Epidemiology
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Vol. 136, No. 10
Printed in U.S.A.

Characteristics Relating to Ovarian Cancer Risk: Collaborative Analysis of 12 US Case-Control Studies

IV. The Pathogenesis of Epithelial Ovarian Cancer

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Two hypotheses have been proposed to explain the reduced risk of epithelial ovarian cancer associated with pregnancy and oral contraceptive use. The first states that some sequelae of ovulation increase the likelihood of malignancy and that pregnancies and oral contraceptives protect by suppressing ovulation. The second hypothesis states that circulating levels of pituitary gonadotropins increase the risk of malignancy and that pregnancies and oral contraceptives protect by suppressing secretion of these hormones. The authors evaluate the two hypotheses in light of combined data from 12 United States case-control studies of epithelial ovarian cancer in white women conducted from 1956 to 1986. While a number of observations support both hypotheses, there are exceptions. Differential risk reduction associated with pregnancy and oral contraceptive use (pregnancy being the more effective in young women and the less effective in older women) conflicts with the first "ovulation" hypothesis, while reduced risk associated with breast feeding and absence of altered risk associated with estrogen replacement therapy conflicts with the second "gonadotropin" hypothesis. Several findings would not have been predicted by either hypothesis, e.g., only weak trends relate cancer risk to age at menarche, and, among older women, no clear trends relate risk to age at menopause. Odds ratio attenuation due to errors in reporting personal characteristics may be responsible for some of these inconsistencies. Multidisciplinary research is needed to clarify the etiologic roles of ovulation and gonadotropin stimulation, both of which may enhance carcinogenesis in the ovarian epithelium. *Am J Epidemiol* 1992;136:1212–20.

gonadotropins; ovarian neoplasms; ovulation; reproduction

Pregnancy and oral contraceptive use are associated with reduced risk of epithelial ovarian cancer. These associations appear to reflect more than a correlation between low

Received for publication August 21, 1991, and in final form July 23, 1992.

Abbreviation: FSH, follicle-stimulating hormone.

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Vol. 136, No. 10
and Public Health Printed in U.S.A.

parity and some form of infertility that predisposes to the disease. Two hypotheses propose direct protective effects of these factors. Fathalla (1, 2) hypothesized that ovarian carcinogenesis involves some mechanical sequelae of ovulation, such as trauma or mitotic stimuli to the ovarian epithelium. This "ovulation" hypothesis suggests that pregnancy and oral contraceptive use protect against ovarian cancer by inhibiting ovulation. Alternatively, Gardner (3) and Stadel (4) hypothesized that exposure of the ovarian epithelium to persistently high circulating levels of pituitary gonadotropins increases the likelihood of malignancy. This "gonadotropin" hypothesis suggests that pregnancy and oral contraceptive use protect against ovarian cancer by inhibiting pituitary secretion of gonadotropins.

Animal experiments provide evidence to support both hypotheses. In domestic fowl, stimulating egg production induces ovarian adenomas (5), and in rodents, anatomic alterations that result in increased gonadotropin secretion enhance ovarian tumorigenesis (6). However, because these experimentally induced tumors are either uncommon or nonexistent in humans, their relevance to the epithelial cancers that comprise the majority of human malignancies is unclear. Here we evaluate the hypotheses in light of combined data from 12 United States case-control studies of epithelial ovarian cancer in white women conducted from 1956 to 1986 and described in the previous two papers.

PREGNANCIES

Pregnancy induces both anovulation and suppression of pituitary gonadotropins (7, 8). Thus, both hypotheses predict that pregnancies reduce ovarian cancer risk. In support of this prediction, each additional term pregnancy (even among the highly parous) is associated with reduced risk of both invasive cancer (9, table 4) and cancers of low malignant potential (10, table 1). The data suggest that each additional pregnancy after the first confers the same percent reduction in risk of invasive cancer, estimated to be about 14 percent. For the population-based studies, this reduction is smaller ($p < 0.001$) than the 40 percent reduction found for the first term pregnancy. In terms of the two hypotheses then, the population-based data suggest that some factor in addition to a period of anovulation or gonadotropin suppression distinguishes uniparous women from nulliparous women.

Both the ovulation and the gonadotropin hypotheses predict that failed pregnancies protect against ovarian cancer, perhaps to a lesser degree than do term pregnancies. The data for both invasive and borderline cancers support this prediction. Failed pregnancies are associated with reduced risk among the parous (9, table 5 and 10, table 1), although no clear effect of gravidity is evident among the nulliparous. The risk reduction per pregnancy is smaller in magnitude for failed pregnancies than for term pregnancies. However, data on gestational length for each pregnancy, available from a subset of the studies, suggest that the decreased protection associated with a failed pregnancy is due to its shorter length: Among the gravid, odds ratios per month of pregnancy do not depend on pregnancy outcome. In conclusion then, findings from the combined data concerning the relation of pregnancies to ovarian cancer risk support both hypotheses.

Both hypotheses, and especially the gonadotropin hypothesis, also receive support from the observed increased risk of both invasive and borderline ovarian cancer associated with use of fertility drugs (9, table 3 and 10, table 1). Such drugs stimulate ovulation by increasing follicular-phase levels of follicle-stimulating hormone (FSH). Clues to pathogenesis are provided by the complications of fertility drugs, which include multiple gestations (supportive of the

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Supported by National Cancer Institute grants CA 43669, CA 47427, and CA 47448.

The authors are grateful to Drs. Sally Glaser, Esther M. John, Pamela Horn-Ross, and Carolyn Westat for helpful comments on earlier versions of the manuscript.

ovulation hypothesis) and ovarian enlargement from FSH hyperstimulation (supportive of the gonadotropin hypothesis) (11, 12).

BREAST FEEDING

Breast feeding induces partial inhibition of ovulation in lactating women (13, 14). Thus,the ovulation hypothesis predicts that breast feeding reduces ovarian cancer risk. Breast feeding also induces increased secretion of FSH and reduced secretion of luteinizing hormone (15). In lactating women, FSH rises after childbirth to normal follicular phase values and remains elevated until the return of ovarian estrogenic function (16). Thus, the gonadotropin hypothesis predicts that breast feeding, with its concomitant elevated FSH levels, increases risk. Yet the data for both invasive cancers (9, table 7) and cancers of low malignant potential (10, table 1) show reduced risk associated with breast feeding. So the data on breast feeding, while consistent with the ovulation hypothesis, conflict with the gonadotropin hypothesis. It should be noted however, that lactation is also associated with ovarian refractoriness to FSH stimulation (15), and this characteristic may be responsible for its apparent protective effect.

The effectiveness of lactation in suppressing ovulation is strongest during the first few months after delivery and wanes thereafter (15). The ovulation hypothesis thus predicts that a month of lactation shortly after delivery reduces a woman's ovarian cancer risk more than does a month of subsequent lactation. Data available from six of the studies support this prediction.

AGE AT MENARCHE AND AGE AT MENOPAUSE

Studies in the United States (17) and Finland (18) suggest that the later menarche occurs the longer it takes to establish regular ovulatory cycles. Thus, the ovulation hypothesis predicts that women who began menstruating before their teens have higher ovarian cancer risk than do women with later menarche because the former started ovulating earlier. By contrast, cessation of menstruation at menopause is a poor surrogate for cessation of ovulation, since ovulatory cycles occur sporadically during the perimenopausal years. The ovulation hypothesis therefore predicts that late age at menopause is weakly associated with increased ovarian cancer risk. In agreement with the prediction for menarche, the data show trends of increased risk associated with early menarche, although the trends are weak (9, table 8). However, in disagreement with the prediction for menopause, the data show no clear trends with later cessation of menstruation (9, table 8 and 10, table 3). Among older women, those with late menopause have no altered risk of invasive cancer in the hospital-based studies and slightly decreased risk in the population-based studies. The slight decrease in risk in the population data supports, instead, the gonadotropin hypothesis because late menopause postpones exposure to elevated gonadotropin levels that accompany the menopause (19). This absence of increasing risk with increasing age at menopause among older women conflicts with the less rapid rise with age of ovarian cancer incidence rates after age 55 years. Such deceleration is seen even in countries where hysterectomy is uncommon and therefore unlikely to bias postmenopausal rates downward by removing women from the population at risk (20, 21).

Imprecision in estimates of age at first and last menses could explain at least some of the discrepancies. Consistent with this interpretation are the stronger trends for menarche and menopause in young women compared with older women, who are less able to recall accurately menstrual events in the distant past (22–24). Indeed, the total age span within which women undergo menopause is relatively narrow, so reporting of menopausal age with large error (23) may misclassify women from one extreme of age at menopause to the other.

EXOGENOUS ESTROGENS

Estrogen-containing oral contraceptives suppress ovulation and reduce pituitary secretion of gonadotropins (25). Thus, both ovulation and gonadotropin hypotheses pre-

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dict that oral contraceptive use reduces ovarian cancer risk. This prediction is supported by trends of decreasing risk with increasing duration of oral contraceptive use, even among the highly parous, as seen in reference 9, table 9 and reference 10, table 2.

Conjugated estrogens also suppress pituitary hormone levels in postmenopausal women, although not to premenopausal levels (25–29). However, the data show no association between estrogen replacement therapy and risk for ovarian cancer, regardless of tumor behavior (9, table 10 and 10, table 2). The failure of estrogen replacement therapy to reduce risk argues against the gonadotropin hypothesis, unless gonadotropin levels in estrogen users are still above a threshold needed to facilitate carcinogenesis.

PELVIC SURGERIES

Tubal ligation and hysterectomy with ovarian conservation may impair ovarian function, possibly by compromising blood supply to the ovaries (30–35). Thus, they should protect against ovarian cancer, according to the ovulation hypothesis. Moreover, hysterectomy during the reproductive years should protect more than hysterectomy after the menopause. These predictions are confirmed by the observed reduced risks associated with both types of surgery (9, table 11 and 10, table 3), although several sources of bias (9) must be considered in interpreting the findings. In contrast, the risk reductions conflict with an increased risk predicted by the gonadotropin hypothesis, unless any estrogen deficiency after surgery (34, 36) fails to elevate gonadotropin levels above a threshold needed for carcinogenesis.

TOTAL YEARS OF ANOVULATION

We next evaluate predictions of the two hypotheses for associations between risk of epithelial ovarian cancer and periods of anovulation and for the variation in strength of these associations with factors such as reference age (i.e., age at diagnosis or interview), source of anovulation, age at anovulation, and adiposity. Here we use the term "anovulation" to mean suppression of menses due to pregnancy, oral contraceptive use, delayed menarche, or early menopause. In this section, we restrict attention to invasive cancers (9), whose numbers were large enough to permit evaluation of such interactions.

Reference age

Pike (37) hypothesized that ovarian cancer incidence rates I are proportional to ovarian epithelial "tissue age" t, measured in units of cell mitoses:

$$I(t) = ct.$$

where c is a constant. Ovulation induces a transient increase in mitotic activity in the ovarian epithelium (1); therefore, a year of anovulation reduces ovarian tissue age by the number t_0 of mitoses avoided. Pike's hypothesis then predicts that each year of anovulation reduces the ovarian cancer incidence rate by a fixed (absolute) amount:

$$I(t) - I(t - t_0) = ct - c(t - t_0) = ct_0.$$

Since a woman's tissue age increases as she ages, the prediction implies that the proportional risk reduction associated with a year of anovulation wanes with age:

$$[I(t) - I(t - t_0)]/I(t) = ct_0/ct \rightarrow 0$$

as t increases. This implication is supported by the attenuated odds ratios among older women (reference age, greater than 55 years) compared with younger women, shown in table 1. This table presents odds ratios among younger and older women according to total years of ovulation, estimated by subtracting age at menarche from age at last menstrual period and then further deducting total time pregnant in term pregnancies (assuming 9 months per pregnancy), breast feeding, or taking oral contraceptives. Women hysterectomized before the menopause were assumed to continue ovulating until age 55 years. Table 1 shows strong and statistically significant trends of increasing risk with increasing years of ovulation for younger, but not older women. The trend in older women showed interstudy heteroge-

TABLE 1. Odds ratios (OR) for invasive epithelial ovarian cancer according to estimated years of ovulation, by reference age

Years of ovulation	Reference age (years)													
	<55†							≥55‡						
	Cases		Controls		OR§	95% CI‖	p value	Cases		Controls		OR§	95% CI	p value
	No.	%	No.	%				No.	%	No.	%			
<25	208	30	2,099	47	1.0			24	5	90	6	1.0		
25–29	131	19	804	18	1.8*	1.4–2.5		24	10	160	11	1.3	0.72–2.3	
30–34	198	29	962	22	2.6*	1.9–3.6		121	23	363	25	1.2	0.72–2.1	
≥35	145	21	595	13	2.9*	2.0–4.1		318	62	826	58	1.5	0.87–2.4	
Overall trend per year					1.08¶		<0.001					1.02#		0.10

*$p < 0.001$.
† Based on studies 2, 6, 8, 9, 11, and 12 (see part I, table 1 (50)).
‡ Based on studies 2, 6, 8, 9, and 12.
§ Adjusted for age and study.
‖ CI, confidence interval.
¶ Test of OR homogeneity across studies: $\chi^2_5 = 5.8$, $p = 0.38$.
# Test of OR homogeneity across studies: $\chi^2_4 = 11.9$, $p = 0.04$.

neity ($p = 0.04$); data from one study showed a stronger trend than did data from the others. Similar trends were obtained when women were classified by the complementary years of anovulation (relative to a maximum 45 years of ovulation for a nulligravid woman with menarche and menopause at ages 10 and 55 years, respectively, who never used oral contraceptives).

In additional age-specific analyses (not shown), measures of risk associated with pregnancy showed strong and consistent trends of attenuation with increasing reference age. Specifically, the percent risk reduction associated with parity relative to nulliparity declined steadily, ranging from 28 percent for women aged less than 40 years to only 1 percent for women aged 70 or more. Indeed, there was little difference in risk by parity among women aged 60 years or more. Similarly, the risk reduction among the parous associated with each term pregnancy declined with age. These trends of decreasing percent risk reduction with increasing age were present ($p < 0.01$) for both hospital- and population-based studies. Such attenuation supports Pike's hypothesis. It also is consistent with a transient protective effect of gonadotropin suppression during pregnancy. However, it contradicts the conjecture that pregnancy induces changes that continue to reduce ovarian cancer risk throughout life. If the conjecture were true, then the percent risk reduction per pregnancy would remain constant or increase, rather than decrease, with age.

The percent risk reduction associated with a year of delayed menarche also tended to wane with increasing reference age, but the trends are more readily explained by chance. Risk reductions associated with breast feeding did not vary by reference age, while those associated with oral contraceptive use showed a nonsignificant increase with age.

Source of anovulation

According to the ovulation hypothesis, ovarian cancer risk depends on a woman's reproductive and menstrual history only as a function of her total years of anovulation, rather than as a function of the individual components from the various sources. Table 2 compares estimates of the percent risk reduction per year of anovulation due to delayed menarche, term pregnancy among the parous, breast feeding among those who had breast-fed, oral contraceptive use among users, and early menopause among those who were naturally postmenopausal or premenopausal. Among younger women, the magnitude of risk reduction per year of term pregnancy exceeds that associated with the other sources. Among older women, how-

ccording to estimated years of

rs)

≥55‡					
es	Controls		OR§	95% CI	p value
%	No.	%			
5	90	6	1.0		
10	160	11	1.3	0.72–2.3	
23	363	25	1.2	0.72–2.1	
62	826	58	1.5	0.87–2.4	
			1.02#		0.10

TABLE 2. Percent reduction of invasive epithelial ovarian cancer risk per year of anovulation according to source, by reference age

Source of anovulation	Reference age (years)			
	<55		≥55	
	% reduction	SE†	% reduction	SE
Delayed‡ menarche	2.1	2.4	0.8	3.0
Term pregnancy§	27.9**	4.3	12.2	5.2
Breast feeding‖	8.5	9.2	10.3	8.7
Oral contraceptive use¶	8.0**	1.7	20.4*	7.9
Early menopause#	−1.0	1.7	0.4	1.0

*$p < 0.01$; **$p < 0.001$.
† SE, standard error.
‡ After age 10 years.
§ Among the parous, adjusted for age, study, and oral contraceptive use, and assuming 9 months per term pregnancy.
‖ Among women who had breast-fed, adjusted for age, study, parity, and oral contraceptive use.
¶ Among users, adjusted for age, study, and parity.
# Before reference age for those aged <55 years and before age 55 years for those aged ≥55. Women with artificial menopause were excluded.

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ever, pregnancy is less protective than is oral contraceptive use. Reporting accuracy is probably greater for time spent pregnant than for time from all other anovulatory sources given in table 2. Since random recall error attenuates regression coefficient estimates toward zero, such error could explain some of the observed differences.

In developed countries, breast feeding suppresses ovulation less effectively than does pregnancy; some 40–75 percent of lactating women menstruate while nursing (13). The findings in table 2 are thus consistent with the ovulation hypothesis, which predicts that a month of breast feeding is associated with a smaller reduction in ovarian cancer risk than is a month of pregnancy.

Although the differences in risk reduction between pregnancy and breast feeding do not achieve statistical significance, those between pregnancy and oral contraceptive use are significant ($p < 0.01$) among younger, but not older women. This difference in risk reduction in younger women, if not due to reporting errors in duration of oral contraceptive use (38) or other bias, conflicts with the ovulation hypothesis, which predicts equal protection per year of pregnancy and oral contraceptive use, since these conditions are equally effective in suppressing ovulation. The difference is more consistent with the gonadotropin hypothesis because the low potency oral contraceptives may be less effective than pregnancy in inhibiting pituitary secretion of gonadotropins (7, 39–41). The relatively large risk reduction associated with oral contraceptive use among older women has a large standard error because few older women had used oral contraceptives. Nevertheless, it suggests that the early high-potency formulations used by these women (42, 43) may be especially protective. Such extra protection also would argue against the ovulation hypothesis since all formulations suppress ovulation at similar rates (44), but would support the gonadotropin hypothesis since the high-dose formulations may have been particularly effective in reducing pituitary gonadotropins (39–41). Alternatively, the large risk reduction accompanying previous oral contraceptive use in older women suggests that the biologic effects of oral contraceptives may increase with time. Like the previous explanation, such a latency effect would conflict with the ovulation hypothesis, but not necessarily with the gonadotropin hypothesis.

The data in table 2 suggest that for all women, neither a year of delayed menarche nor a year of early menopause is associated with the same risk reduction as is a year of pregnancy, breast feeding, or oral contraceptive use. Among younger women, breast feeding and oral contraceptive use appear equally effective in reducing ovarian cancer risk, albeit less effective than pregnancy.

Age at anovulation

The probability that a menstrual cycle is ovulatory varies with age, being highest in the age range 25–40 years and lowest at either end of the reproductive years (45). Thus, the ovulation hypothesis predicts less protection per year of menses suppression due to delayed menarche and early menopause than per year of such suppression at the height of reproductive life. The differences in table 2 support this prediction. Further, since women with late first birth tend to complete their childbearing later than do women with early first birth, the ovulation hypothesis predicts less protection per pregnancy to women with late first birth than to women with early first birth. This second prediction received weak support from the hospital-based data, but not from the population-based data. Future studies should obtain the timing of all pregnancies and episodes of lactation and oral contraceptive use, as well as information on menstrual cycle length, in order to compare ovarian cancer risk reduction per unit time at the height of the reproductive years with that at either extreme.

Adiposity

Extreme obesity before the menopause is associated with increased incidence of anovulatory cycles (46) and lower circulating levels of pituitary gonadotropins (47). Thus, both hypotheses predict that pregnancy, lactation, and oral contraceptive use are more protective to the lean than to the obese, for whom they prevent fewer ovulations and less exposure to FSH. Only the data for breast feeding support this prediction; the risk reductions associated with pregnancy and oral contraceptive use did not vary with adiposity. However, the reduction associated with breast feeding was confined to women whose "usual" value of Quetelet index was less than 35 ($p < 0.05$ for both hospital-based and population-based studies).

SUMMARY

The data relating ovarian cancer risk to pregnancies, oral contraceptive use, and use of fertility drugs support both ovulation and gonadotropin hypotheses. Yet there are inconsistencies: The observed protective effect of delayed menarche is weaker than predicted by either hypothesis, and the lack of clear trends with age at menopause, if not due to recall error or other bias, argues against both hypotheses. The greater risk reduction associated with pregnancy than with oral contraceptive use argues against the ovulation, but not the gonadotropin, hypothesis. Some of these inconsistencies may be due to differential measurement error among the sources, since pregnancies probably are recalled more accurately. Evaluation of this issue in cohort studies is of interest in light of evidence (21, 22) that contemporaneous report of menopausal status and estrogen use may be more accurate than recall of these events later in life.

The findings for breast feeding, estrogen replacement therapy, and pelvic surgeries are consistent with the ovulation hypothesis, but conflict with the gonadotropin hypothesis. However, the endocrine profiles associated with these characteristics and their contributions to ovarian carcinogenesis are poorly understood. Pending further research to clarify these issues, the findings cannot be interpreted as strong evidence against the gonadotropin hypothesis.

Both hypotheses may be valid, with each explaining some fraction of all epithelial ovarian cancers. Histology-specific analysis, although not feasible for these data, may help to distinguish the relative contributions of each. Research involving both epidemiology and the basic sciences will be needed. For example, ovarian cancer has a strong familial component (48), and work is under way to determine genetic loci that predispose to the disease. Markers of genetic susceptibility will permit refined analyses that may elucidate mechanisms. Clinical research will also be useful. For example, epithelial ovarian cancers have been observed in dysgenetic gonads that lack ova and are, therefore, incapable of ovulating (49). This observation demonstrates that ovulation is not necessary for epithelial carcinogenesis. However, dysgenetic gonads are exposed to elevated cir-

culating levels of pituitary gonadotropins and contain binding sites to gonadotropins.

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